ENABLEX- darifenacin tablet, extended release
Allergan, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ENABLEX safely and effectively. See full prescribing information for ENABLEX.

ENABLEX ® (darifenacin) extended-release tablets
Initial U.S. Approval: 2004

INDICATIONS AND USAGE

Enablex is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency (1)

DOSAGE AND ADMINISTRATION

The recommended starting dose of Enablex extended-release tablets is 7.5 mg once daily. Based upon individual response, the dose may be increased to 15 mg once daily, as early as two weeks after starting therapy (2)
The daily dose of Enablex should not exceed 7.5 mg in the following patients:

- Patients with moderate hepatic impairment (Child-Pugh B) (2, 8.6)
- Patients taking potent CYP3A4 inhibitors (2, 7.1)

Enablex is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) (2, 8.6)
Enablex may be taken with or without food. The tablet should be swallowed whole with water and not chewed, divided or crushed (2)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets 7.5 mg and 15 mg (3)

CONTRAINDICATIONS

Enablex is contraindicated in patients with, or at risk for, the following conditions (4):

- urinary retention,
- gastric retention, or
- uncontrolled narrow-angle glaucoma.

WARNINGS AND PRECAUTIONS

- Enablex should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (5.1)
- Enablex should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (5.2)
- Enablex should be used with caution in patients being treated for narrow-angle glaucoma and only where the potential benefits outweigh the risks (5.3)
- Central Nervous System Effects: Somnolence has been reported with Enablex. Advise patients not to drive or operate heavy machinery until they know how Enablex affects them (5.5)

ADVERSE REACTIONS

The most frequently reported adverse reactions (greater than 3%) for Enablex are: constipation, dry mouth, headache, dyspepsia, nausea, urinary tract infection, accidental injury, and flu symptoms (6)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Caution should be taken when Enablex is used concomitantly with medications that are predominantly metabolized by CYP2D6 and which have a narrow therapeutic window, such as flecainide, thioridazine and tricyclic antidepressants (7.2)
- The concomitant use of Enablex with other anticholinergic agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision and other anticholinergic pharmacological effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to effects of gastrointestinal motility (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Enablex should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus (8.1)

- Nursing Mothers: It is not known whether darifenacin is excreted into human milk and therefore caution should be exercised before Enablex is administered to a nursing woman (8.3)
- Pediatric Use: The safety and effectiveness of Enablex in pediatric patients have not been established (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Enablex (darifenacin) is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.

2 DOSAGE AND ADMINISTRATION

The recommended starting dose of Enablex is 7.5 mg once daily. Based upon individual response, the dose may be increased to 15 mg once daily, as early as two weeks after starting therapy.

Enablex should be taken once daily with water. Enablex may be taken with or without food, and should be swallowed whole and not chewed, divided or crushed.

For patients with moderate hepatic impairment (Child-Pugh B) or when co-administered with potent CYP3A4 inhibitors (for example, ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin and nefazadone), the daily dose of Enablex should not exceed 7.5 mg. Enablex is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) *[see Warnings & Precautions (5.6), Drug Interactions (7.1), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Enablex extended-release tablets 7.5 mg are round, shallow, bi-convex, white-colored tablets, and are identified with “DF” on one side and “7.5” on the reverse.

Enablex extended-release tablets 15 mg are round, shallow, bi-convex, light peach-colored tablets, and are identified with “DF” on one side and “15” on the reverse.

4 CONTRAINDICATIONS

Enablex is contraindicated in patients with, or at risk for, the following conditions:

- urinary retention
- gastric retention, or
- uncontrolled narrow-angle glaucoma.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Urinary Retention

Enablex should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

5.2 Decreased Gastrointestinal Motility

Enablex should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention. Enablex, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as severe constipation, ulcerative colitis, and myasthenia gravis.

5.3 Controlled Narrow-Angle Glaucoma

Enablex should be used with caution in patients being treated for narrow-angle glaucoma and only where the potential benefits outweigh the risks.

5.4 Angioedema

Angioedema of the face, lips, tongue, and/or larynx have been reported with darifenacin. In some cases angioedema occurred after the first dose. Angioedema associated with upper airway swelling may be life threatening. If involvement of the tongue, hypopharynx, or larynx occurs, darifenacin should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

5.5 Central Nervous System Effects

Enablex is associated with anticholinergic central nervous system (CNS) effects *[see Adverse Reactions (6.2)]*. A variety of CNS anticholinergic effects have been reported, including headache, confusion, hallucinations and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until they know how Enablex affects them. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

5.6 Patients with Hepatic Impairment

The daily dose of Enablex should not exceed 7.5 mg for patients with moderate hepatic impairment (Child-Pugh B). Enablex has not been studied in patients with severe hepatic impairment (Child-Pugh C) and therefore is not recommended for use in this patient population *[see Dosage and Administration (2) Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Enablex was evaluated in controlled clinical trials in a total of 8,830 patients, 6,001 of whom were treated with Enablex. Of this total, 1,069 patients participated in three, 12-week, randomized, placebo-controlled, fixed-dose efficacy and safety studies (Studies 1, 2 and 3). Of this total, 337 and 334 patients received Enablex 7.5 mg daily and 15 mg daily, respectively. In all long-term trials combined, 1,216 and 672 patients received treatment with Enablex for at least 24 and 52 weeks, respectively.

In Studies 1, 2 and 3 combined, the serious adverse reactions to Enablex were urinary retention and constipation.

In Studies 1, 2 and 3 combined, dry mouth leading to study discontinuation occurred in 0%, 0.9%, and 0% of patients treated with Enablex 7.5 mg daily, Enablex 15 mg daily and placebo, respectively. Constipation leading to study discontinuation occurred in 0.6%, 1.2%, and 0.3% of patients treated with Enablex 7.5 mg daily, Enablex 15 mg daily and placebo, respectively.

Table 1 lists the rates of identified adverse reactions, derived from all reported adverse events in 2% or more of patients treated with 7.5 mg or 15 mg Enablex, and greater than placebo in Studies 1, 2 and 3. In these studies, the most frequently reported adverse reactions were dry mouth and constipation. The majority of the adverse reactions were mild or moderate in severity and most occurred during the first two weeks of treatment.

Table 1: Incidence of Identified Adverse Reactions, Derived from All Adverse Events Reported

in greater than or equal to 2% of Patients Treated with Enablex Extended-Release Tablets and More Frequent with Enablex than with Placebo in Studies 1, 2, and 3

Body System	Adverse Reaction	% of Subjects		
		Enablex 7.5 mg N = 337	Enablex 15 mg N = 334	Placebo N = 388
Digestive	Dry Mouth	20.2	35.3	8.2
	Constipation	14.8	21.3	6.2
	Dyspepsia	2.7	8.4	2.6
	Abdominal Pain	2.4	3.9	0.5
	Nausea	2.7	1.5	1.5
	Diarrhea	2.1	0.9	1.8
Urogenital	Urinary Tract Infection	4.7	4.5	2.6
Nervous	Dizziness	0.9	2.1	1.3
Body as a Whole	Asthenia	1.5	2.7	1.3
Eye	Dry Eyes	1.5	2.1	0.5

Other adverse reactions reported by 1% to 2% of Enablex-treated patients include: abnormal vision, accidental injury, back pain, dry skin, flu syndrome, hypertension, vomiting, peripheral edema, weight gain, arthralgia, bronchitis, pharyngitis, rhinitis, sinusitis, rash, pruritus, urinary tract disorder and vaginitis.

Study 4 was a randomized, 12-week, placebo-controlled, dose-titration regimen study in which Enablex was administered in accordance with dosing recommendations *[see Dosage and Administration (2)]*. All patients initially received placebo or Enablex 7.5 mg daily, and after two weeks, patients and physicians were allowed to adjust upward to Enablex 15 mg if needed. In this study, the most commonly reported adverse reactions were also constipation and dry mouth. Table 2 lists the identified adverse reactions, derived from all adverse events reported in greater than 3% of patients treated with Enablex and greater than placebo.

Table 2: Number (%) of Adverse Reactions, Derived from All Adverse Events Reported in greater than 3% of Patients Treated with Enablex Extended-Release Tablets, and More Frequent with Enablex than Placebo, in Study 4

Adverse Reaction	Enablex 7.5 mg/15 mg N = 268	Placebo N = 127
Constipation	56 (20.9%)	10 (7.9%)

Dry Mouth	50 (18.7%)	11 (8.7%)
Headache	18 (6.7%)	7 (5.5%)
Dyspepsia	12 (4.5%)	2 (1.6%)
Nausea	11 (4.1%)	2 (1.6%)
Urinary Tract Infection	10 (3.7%)	4 (3.1%)
Accidental Injury	8 (3.0%)	3 (2.4%)
Flu Syndrome	8 (3.0%)	3 (2.4%)

6.2 Post Marketing Experience

The following adverse reactions have been reported during post-approval use of Enablex extended-release tablets (darifenacin). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure.

Dermatologic: erythema multiforme, interstitial granuloma annulare

General: hypersensitivity reactions, including angioedema with airway obstruction and anaphylactic reaction

Central Nervous: confusion, hallucinations and somnolence

Cardiovascular: palpitations and syncope

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors

The systemic exposure of darifenacin from Enablex extended-release tablets is increased in the presence of CYP3A4 inhibitors. The daily dose of Enablex should not exceed 7.5 mg when co-administered with potent CYP3A4 inhibitors (for example, ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin and nefazadone). No dosing adjustments are recommended in the presence of moderate CYP3A4 inhibitors (for example, erythromycin, fluconazole, diltiazem and verapamil) *[see Dosage and Administration (2) and Clinical Pharmacology (12.3)]*.

7.2 CYP2D6 Inhibitors

No dosing adjustments are recommended in the presence of CYP2D6 inhibitors (for example, paroxetine, fluoxetine, quinidine and duloxetine) *[see Clinical Pharmacology (12.3)]*.

7.3 CYP2D6 Substrates

Caution should be taken when Enablex is used concomitantly with medications that are predominantly metabolized by CYP2D6 and which have a narrow therapeutic window (for example, flecainide, thioridazine and tricyclic antidepressants) *[see Clinical Pharmacology (12.3)]*.

7.4 CYP3A4 Substrates

Darifenacin (30 mg daily) did not have a significant impact on midazolam (7.5 mg) pharmacokinetics *[see Clinical Pharmacology (12.3)]*.

7.5 Combination oral contraceptives

Darifenacin (10 mg three times daily) had no effect on the pharmacokinetics of the combination oral contraceptives containing levonorgestrel and ethinyl estradiol *[see Clinical Pharmacology (12.3)]*.

7.6 Warfarin

Darifenacin had no significant effect on prothrombin time when a single dose of warfarin 30 mg was co-administered with darifenacin (30 mg daily) at steady-state. Standard therapeutic prothrombin time monitoring for warfarin should be continued.

7.7 Digoxin

Darifenacin (30 mg daily) did not have a clinically relevant effect on the pharmacokinetics of digoxin (0.25 mg) at steady-state. Routine therapeutic drug monitoring for digoxin should be continued *[see Clinical Pharmacology (12.3)]*.

7.8 Other Anticholinergic Agents

The concomitant use of Enablex with other anticholinergic agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision and other anticholinergic pharmacological effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to effects on gastrointestinal motility.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no studies of darifenacin in pregnant women.

Darifenacin was not teratogenic in rats and rabbits at plasma exposures of free drug (via AUC) up to 59 times and 28 times, respectively (doses up to 50 and 30 mg/kg/day, respectively) the maximum recommended human dose [MRHD] of 15 mg. At approximately 59 times the MRHD in rats, there was a delay in the ossification of the sacral and caudal vertebrae which was not observed at approximately 13 times the AUC. Dystocia was observed in dams at approximately 17 times the AUC (10 mg/kg/day). Slight developmental delays were observed in pups at this dose. At five times the AUC (3 mg/kg/day), there were no effects on dams or pups. In rabbits, an exposure approximately 28 times (30 mg/kg/day) the MRHD of darifenacin was shown to increase post-implantation loss, with a no effect level at nine times (10 mg/kg/day) the AUC at the MRHD. Dilated ureter and/or kidney pelvis was also observed in offspring at this dose along with urinary bladder dilation consistent with the pharmacological action of darifenacin, with one case observed at nine times (10 mg/kg/day). No effect was observed at approximately 2.8 times (3 mg/kg/day) the AUC at the MRHD.

Because animal reproduction studies are not always predictive of human response, Enablex should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus.

8.3 Nursing Mothers

Darifenacin is excreted into the milk of rats. It is not known whether darifenacin is excreted into human milk and therefore caution should be exercised before Enablex is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of Enablex in pediatric patients have not been established.

8.5 Geriatric Use

In the fixed-dose, placebo-controlled, clinical studies, 30% of patients treated with Enablex were over 65 years of age. No overall differences in safety or efficacy were observed between patients over 65 years (n = 207) and younger patients less than 65 years (n = 464). No dose adjustment is recommended for elderly patients *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

8.6 Hepatic Impairment

Subjects with severe hepatic impairment (Child-Pugh C) have not been studied, therefore Enablex is not recommended for use in these patients *[see Dosage and Administration (2) and Warnings and Precautions (5.6)]*. The daily dose of Enablex should not exceed 7.5 mg once daily for patients with moderate hepatic impairment (Child-Pugh B) *[see Dosage and Administration (2) and Warnings and Precautions (5.6)]*. After adjusting for plasma protein binding, unbound darifenacin exposure was estimated to be 4.7-fold higher in subjects with moderate hepatic impairment than subjects with normal hepatic function. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).

8.7 Renal Impairment

A study of subjects with varying degrees of renal impairment (creatinine clearance between 10 and 136 mL/min) demonstrated no clear relationship between renal function and darifenacin clearance. No dose adjustment is recommended for patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

8.8 Gender

No dose adjustment is recommended based on gender *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

10 OVERDOSAGE

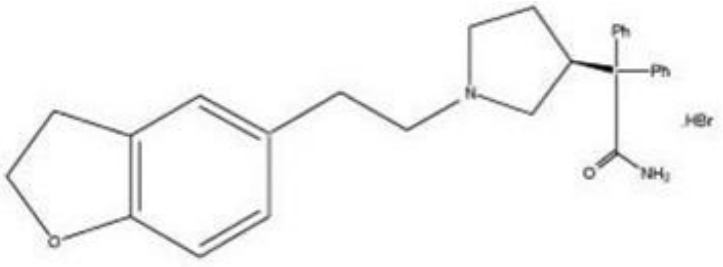
Overdosage with antimuscarinic agents, including Enablex, can result in severe antimuscarinic effects. Treatment should be symptomatic and supportive. In the event of overdosage, ECG monitoring is recommended. Enablex has been administered in clinical trials at doses up to 75 mg (five times the maximum therapeutic dose) and signs of overdose were limited to abnormal vision.

11 DESCRIPTION

Enablex is an extended-release tablet for oral administration which contains 7.5 mg or 15 mg darifenacin as its hydrobromide salt. The active moiety, darifenacin, is a potent muscarinic receptor antagonist.

Chemically, darifenacin hydrobromide is *(S)*-2-{1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide hydrobromide. The empirical formula of darifenacin hydrobromide is $C_{28}H_{30}N_2O_2$•HBr.

The structural formula is:



Darifenacin hydrobromide is a white to almost white, crystalline powder, with a molecular weight of 507.5.

Enablex is a once-a-day extended-release tablet and contains the following inactive ingredients: dibasic calcium phosphate anhydrous, hypromellose, magnesium stearate, polyethylene glycol, talc, titanium

dioxide. The 15 mg tablet also contains ferric oxide red and ferric oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Darifenacin is a competitive muscarinic receptor antagonist. Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of the urinary bladder smooth muscle and stimulation of salivary secretion.

In vitro studies using human recombinant muscarinic receptor subtypes show that darifenacin has greater affinity for the M_3 receptor than for the other known muscarinic receptors (9- and 12-fold greater affinity for M_3 compared to M_1 and M_5, respectively, and 59-fold greater affinity for M_3 compared to both M_2 and M_4). M_3 receptors are involved in contraction of human bladder and gastrointestinal smooth muscle, saliva production, and iris sphincter function. Adverse drug effects such as dry mouth, constipation and abnormal vision may be mediated through effects on M_3 receptors in these organs.

12.2 Pharmacodynamics

In three cystometric studies performed in patients with involuntary detrusor contractions, increased bladder capacity was demonstrated by an increased volume threshold for unstable contractions and diminished frequency of unstable detrusor contractions after Enablex treatment. These findings are consistent with an antimuscarinic action on the urinary bladder.

Electrophysiology

The effect of a six-day treatment of 15 mg and 75 mg Enablex on QT/QTc interval was evaluated in a multiple-dose, double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg) parallel-arm design study in 179 healthy adults (44% male, 56% female) aged 18 to 65. Subjects included 18% poor metabolizers (PMs) and 82% extensive metabolizers (EMs). The QT interval was measured over a 24-hour period both predosing and at steady-state. The 75 mg Enablex dose was chosen because this achieves exposure similar to that observed in CYP2D6 poor metabolizers administered the highest recommended dose (15 mg) of darifenacin in the presence of a potent CYP3A4 inhibitor. At the doses studied, Enablex did not result in QT/QTc interval prolongation at any time during the steady-state, while moxifloxacin treatment resulted in a mean increase from baseline QTcF of about 7.0 msec when compared to placebo. In this study, darifenacin 15 mg and 75 mg doses demonstrated a mean heart rate change of 3.1 and 1.3 bpm, respectively, when compared to placebo. However, in the clinical efficacy and safety studies, the change in median HR following treatment with Enablex was no different from placebo.

12.3 Pharmacokinetics

Absorption

After oral administration of Enablex to healthy volunteers, peak plasma concentrations of darifenacin are reached approximately seven hours after multiple dosing and steady-state plasma concentrations are achieved by the sixth day of dosing. The mean (SD) steady-state time course of Enablex 7.5 mg and 15 mg extended-release tablets is depicted in Figure 1.

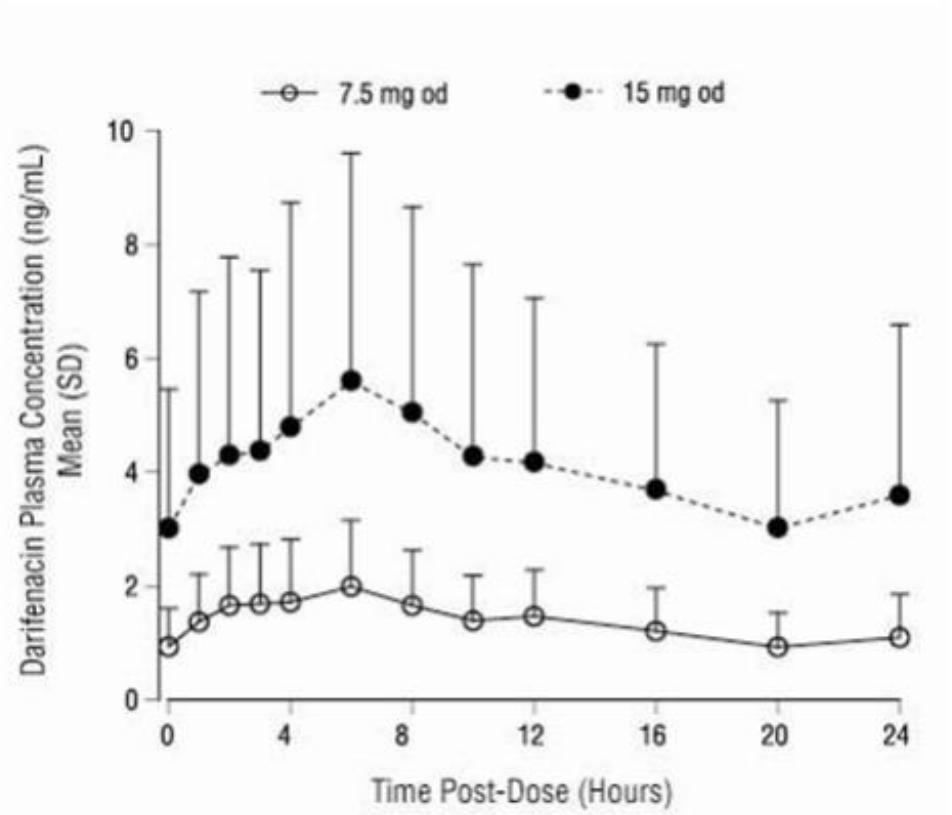


Figure 1 Mean (SD) Steady-State Darifenacin Plasma Concentration-Time Profiles for Enablex 7.5 mg and 15 mg in Healthy Volunteers Including Both CYP2D6 EMs and PMs*

*Includes 95 EMs and 6 PMs for 7.5 mg; 104 EMs and 10 PMs for 15 mg.

A summary of mean (standard deviation, SD) steady-state pharmacokinetic parameters of Enablex 7.5 mg and 15 mg extended-release tablets in EMs and PMs of CYP2D6 is provided in Table 3.

Table 3: Mean (SD) Steady-State Pharmacokinetic Parameters from Enablex 7.5 mg and 15 mg Extended-Release Tablets Based on Pooled Data by Predicted CYP2D6 Phenotype

	Enablex 7.5 mg (N = 68 EM, 5 PM)					**Enablex 15 mg (N = 102 EM, 17 PM)**				
	AUC_{24} (ng•h/mL)	**C_{max} (ng/mL)**	**C_{avg} (ng/mL)**	**T_{max} (h)**	**$t_{1/2}$ (h)**	**AUC_{24} (ng•h/mL)**	**C_{max} (ng/mL)**	**C_{avg} (ng/mL)**	**T_{max} (h)**	**$t_{1/2}$ (h)**
EM	29.24 (15.47)	2.01 (1.04)	1.22 (0.64)	6.49 (4.19)	12.43 (5.64)[a]	88.90 (67.87)	5.76 (4.24)	3.70 (2.83)	7.61 (5.06)	12.05 (12.37)[b]
PM	67.56 (13.13)	4.27 (0.98)	2.81 (0.55)	5.20 (1.79)	19.95[c] -	157.71 (77.08)	9.99 (5.09)	6.58 (3.22)	6.71 (3.58)	7.40[d] -

[a]N = 25; [b]N = 8; [c]N = 2; [d]N = 1; AUC_{24} = Area under the plasma concentration versus time curve for 24h;

C_{max} = Maximum observed plasma concentration; C_{avg} = Average plasma concentration at steady-state;

T_{max} = Time of occurrence of C_{max}; $t_{1/2}$ = Terminal elimination half-life. Regarding EM and PM *[see Clinical Pharmacology, Pharmacokinetics, Variability in Metabolism (12.3)]*.

The mean oral bioavailability of Enablex in EMs at steady-state is estimated to be 15% and 19% for 7.5 mg and 15 mg tablets, respectively.

Effect of Food

Following single dose administration of Enablex with food, the AUC of darifenacin was not affected, while the C_{max} was increased by 22% and T_{max} was shortened by 3.3 hours. There is no effect of food on multiple-dose pharmacokinetics from Enablex.

Distribution

Darifenacin is approximately 98% bound to plasma proteins (primarily to alpha-1-acid-glycoprotein). The steady-state volume of distribution (V_{ss}) is estimated to be 163 L.

Metabolism

Darifenacin is extensively metabolized by the liver following oral dosing.

Metabolism is mediated by cytochrome P450 enzymes CYP2D6 and CYP3A4. The three main metabolic routes are as follows:

(i) monohydroxylation in the dihydrobenzofuran ring;
(ii) dihydrobenzofuran ring opening;
(iii) N-dealkylation of the pyrrolidine nitrogen.

The initial products of the hydroxylation and N-dealkylation pathways are the major circulating metabolites but they are unlikely to contribute significantly to the overall clinical effect of darifenacin.

Variability in Metabolism

A subset of individuals (approximately 7% Caucasians and 2% African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. Individuals with normal CYP2D6 activity are referred to as extensive metabolizers (EMs). The metabolism of darifenacin in PMs will be principally mediated via CYP3A4. The darifenacin ratios (PM versus EM) for C_{max} and AUC following darifenacin 15 mg once daily at steady-state were 1.9 and 1.7, respectively.

Excretion

Following administration of an oral dose of ^{14}C-darifenacin solution to healthy volunteers, approximately 60% of the radioactivity was recovered in the urine and 40% in the feces. Only a small percentage of the excreted dose was unchanged darifenacin (3%). Estimated darifenacin clearance is 40 L/h for EMs and 32 L/h for PMs. The elimination half-life of darifenacin following chronic dosing is approximately 13 to 19 hours.

Drug-Drug Interactions

Effects of Other Drugs on Darifenacin

Darifenacin metabolism is primarily mediated by the cytochrome P450 enzymes CYP2D6 and CYP3A4. Therefore, inducers of CYP3A4 or inhibitors of either of these enzymes may alter darifenacin pharmacokinetics *[see Drug Interactions (7)]*.

CYP3A4 Inhibitors: In a drug interaction study, when a 7.5 mg once daily dose of Enablex was given to steady-state and co-administered with the potent CYP3A4 inhibitor ketoconazole 400 mg, mean darifenacin C_{max} increased to 11.2 ng/mL for EMs (n = 10) and 55.4 ng/mL for one PM subject (n = 1). Mean AUC increased to 143 and 939 ng•h/mL for EMs and for one PM subject, respectively. When a 15 mg daily dose of Enablex was given with ketoconazole, mean darifenacin C_{max} increased to 67.6 ng/mL and 58.9 ng/mL for EMs (n = 3) and one PM subject (n = 1), respectively. Mean AUC increased to 1110 and 931 ng•h/mL for EMs and for one PM subject, respectively *[see Dosage and*

Administration (2) and Drug Interactions (7.1)].

The mean C_{max} and AUC of darifenacin following 30 mg once daily dosing at steady-state were 128% and 95% higher, respectively, in the presence of a moderate CYP3A4 inhibitor, erythromycin. Co-administration of fluconazole, a moderate CYP3A4 inhibitor and darifenacin 30 mg once daily at steady-state increased darifenacin C_{max} and AUC by 88% and 84%, respectively *[see Drug Interactions (7.1)]*.

The mean C_{max} and AUC of darifenacin following 30 mg once daily at steady-state were 42% and 34% higher, respectively, in the presence of cimetidine, a mixed CYP P450 enzyme inhibitor.

CYP2D6 Inhibitors: Darifenacin exposure following 30 mg once daily at steady-state was 33% higher in the presence of the potent CYP2D6 inhibitor paroxetine 20 mg *[see Drug Interactions (7.2)]*.

Effects of Darifenacin on Other Drugs

In Vitro Studies: Based on *in vitro* human microsomal studies, Enablex is not expected to inhibit CYP1A2 or CYP2C9 at clinically relevant concentrations.

In Vivo Studies: The potential for clinical doses of Enablex to act as inhibitors of CYP2D6 or CYP3A4 substrates was investigated in specific drug interaction studies.

CYP2D6 Substrates: The mean C_{max} and AUC of imipramine, a CYP2D6 substrate, were increased by 57% and 70%, respectively, in the presence of steady-state darifenacin 30 mg once daily. The mean C_{max} and AUC of desipramine, the active metabolite of imipramine, were increased by 260% *[see Drug Interactions (7.3)]*.

CYP3A4 Substrates: Darifenacin (30 mg daily) co-administered with a single oral dose of midazolam 7.5 mg resulted in a 17% increase in midazolam exposure.

Combination Oral Contraceptives: Darifenacin (10 mg three times daily) had no effect on the pharmacokinetics of a combination oral contraceptive containing levonorgestrel (0.15 mg) and ethinyl estradiol (0.03 mg).

Warfarin: Darifenacin had no significant effect on prothrombin time when a single dose of warfarin 30 mg was co-administered with darifenacin (30 mg daily) at steady-state *[see Drug Interactions (7.6)]*.

Digoxin: Darifenacin (30 mg daily) co-administered with digoxin (0.25 mg) at steady-state resulted in a 16% increase in digoxin exposure *[see Drug Interactions (7.7)]*.

Pharmacokinetics in Special Populations

Age: A population pharmacokinetic analysis of patient data indicated a trend for clearance of darifenacin to decrease with age (6% per decade relative to a median age of 44). Following administration of Enablex 15 mg once daily, darifenacin exposure at steady-state was approximately 12% to 19% higher in volunteers between 45 and 65 years of age compared to younger volunteers aged 18 to 44 years *[see Use in Specific Populations (8.5)]*.

Pediatric: The pharmacokinetics of Enablex has not been studied in the pediatric population *[see Use in Specific Populations (8.4)]*.

Gender: PK parameters were calculated for 22 male and 25 female healthy volunteers. Darifenacin C_{max} and AUC at steady-state were approximately 57% to 79% and 61% to 73% higher in females than in males, respectively *[see Use in Specific Populations (8.8)]*.

Renal Impairment: A study of subjects with varying degrees of renal impairment (creatinine clearance between 10 and 136 mL/min) given Enablex 15 mg once daily to steady-state demonstrated no clear relationship between renal function and darifenacin clearance *[see Use in Specific Populations (8.7)]*.

Hepatic Impairment: Enablex pharmacokinetics were investigated in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) impairment of hepatic function given Enablex 15 mg once daily to steady-state. Mild hepatic impairment had no effect on the pharmacokinetics of darifenacin. However, protein binding of darifenacin was affected by moderate hepatic impairment. After adjusting for plasma protein

binding, unbound darifenacin exposure was estimated to be 4.7-fold higher in subjects with moderate hepatic impairment than subjects with normal hepatic function. Subjects with severe hepatic impairment (Child-Pugh C) have not been studied *[see Dosage and Administration (2), Warning and Precautions (5.5) and Use in Specific Population (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with darifenacin were conducted in mice and rats. No evidence of drug-related carcinogenicity was revealed in a 24-month study in mice at dietary doses up to 100 mg/kg/day or approximately 32 times the estimated free plasma AUC reached at the maximum recommended human dose (the AUC at the MRHD) of 15 mg and in a 24-month study in rats at doses up to 15 mg/kg/day or up to approximately 12 times the AUC at the MRHD in female rats and approximately eight times the AUC at the MRHD in male rats.

Darifenacin was not genotoxic in the bacterial mutation assay (Ames test), the Chinese hamster ovary assay, the human lymphocyte assay, or the *in vivo* mouse bone marrow cytogenetics assay.

There was no evidence for effects on fertility in male or female rats treated at oral doses up to approximately 78 times (50 mg/kg/day) the AUC at the MRHD.

14 CLINICAL STUDIES

Enablex extended-release tablets were evaluated for the treatment of patients with overactive bladder with symptoms of urgency, urge urinary incontinence, and increased urinary frequency in three randomized, fixed-dose, placebo-controlled, multicenter, double-blind, 12-week studies (Studies 1, 2 and 3) and one randomized, double-blind, placebo-controlled, multicenter, dose-titration study (Study 4). For study eligibility in all four studies, patients with symptoms of overactive bladder for at least six months were required to demonstrate at least eight micturitions and at least one episode of urinary urgency per day, and at least five episodes of urge urinary incontinence per week. The majority of patients were white (94%) and female (84%), with a mean age of 58 years, range 19 to 93 years. Thirty-three percent of patients were greater than or equal to 65 years of age. These characteristics were well balanced across treatment groups. The study population was inclusive of both naïve patients who had not received prior pharmacotherapy for overactive bladder (60%) and those who had (40%).

Table 4 shows the efficacy data collected from 7- or 14-day voiding diaries in the three fixed-dose placebo-controlled studies of 1,059 patients treated with placebo, 7.5 mg or 15 mg once daily Enablex for 12 weeks. A significant decrease in the primary endpoint, change from baseline in average weekly urge urinary incontinence episodes was observed in all three studies. Data is also shown for two secondary endpoints, change from baseline in the average number of micturitions per day (urinary frequency) and change from baseline in the average volume voided per micturition.

Table 4: Difference Between Enablex (7.5 mg, 15 mg) and Placebo for the Week 12 Change from Baseline (Studies 1, 2 and 3)

	Study 1			**Study 2**			**Study 3**	
	Enablex 7.5 mg	**Enablex 15 mg**	**Placebo**	**Enablex 7.5 mg**	**Enablex 15 mg**	**Placebo**	**Enablex 15 mg**	**Placebo**
No. of Patients Entered	229	115	164	108	107	109	112	115

Urge Incontinence Episodes per Week								
Median Baseline	16.3	17.0	16.6	14.0	17.3	16.1	16.2	15.5
Median Change from Baseline	-9.0	-10.4	-7.6	-8.1	-10.4	-5.9	-11.4	-9.0
Median Difference to Placebo	-1.5*	-2.1*	-	-2.8*	-4.3*	-	-2.4*	-
Micturitions per Day								
Median Baseline	10.1	10.1	10.1	10.3	11.0	10.1	10.5	10.4
Median Change from Baseline	-1.6	-1.7	-0.8	-1.7	-1.9	-1.1	-1.9	-1.2
Median Difference to Placebo	-0.8*	-0.9*	-	-0.5	-0.7*	-	-0.5	-
Volume of Urine Passed per Void (mL)								
Median Baseline	160.2	151.8	162.4	161.7	157.3	162.2	155.0	147.1
Median Change from Baseline	14.9	30.9	7.6	16.8	23.6	7.1	26.7	4.6
Median Difference to Placebo	9.1*	20.7*	-	9.2	16.6*	-	20.1*	-

*Indicates statistically significant difference versus placebo (p less than 0.05, Wilcoxon rank-sum test)

Table 5 shows the efficacy data from the dose-titration study in 395 patients who initially received 7.5 mg Enablex or placebo daily with the option to increase to 15 mg Enablex or placebo daily after two weeks.

Table 5: Difference between Enablex (7.5 mg/15 mg) and Placebo for the Week 12 Change from Baseline (Study 4)

	Enablex 7.5 mg /15 mg	**Placebo**
No. of Patients Treated	268	127

Urge Incontinence Episodes per Week		
Median Baseline	16.0	14.0
Median Change from Baseline	-8.2	-6.0
Median Difference to Placebo	-1.4*	-
Micturitions per Day		
Median Baseline	9.9	10.4
Median Change from Baseline	-1.9	-1.0
Median Difference to Placebo	-0.8*	-
Volume of Urine Passed per Void (mL)		
Median Baseline	173.7	177.2
Median Change from Baseline	18.8	6.6
Median Difference to Placebo	13.3*	-
*Indicates statistically significant difference versus placebo (p less than 0.05, Wilcoxon rank-sum test)		

As seen in Figures 2a, 2b and 2c, reductions in the number of urge incontinence episodes per week were observed within the first two weeks in patients treated with Enablex 7.5 mg and 15 mg once daily compared to placebo. Further, these effects were sustained throughout the 12-week treatment period.

Figures 2a, 2b, 2c. Median Change from Baseline at Weeks 2, 6, 12 for Number of Urge Incontinence Episodes per Week (Studies 1, 2 and 3)

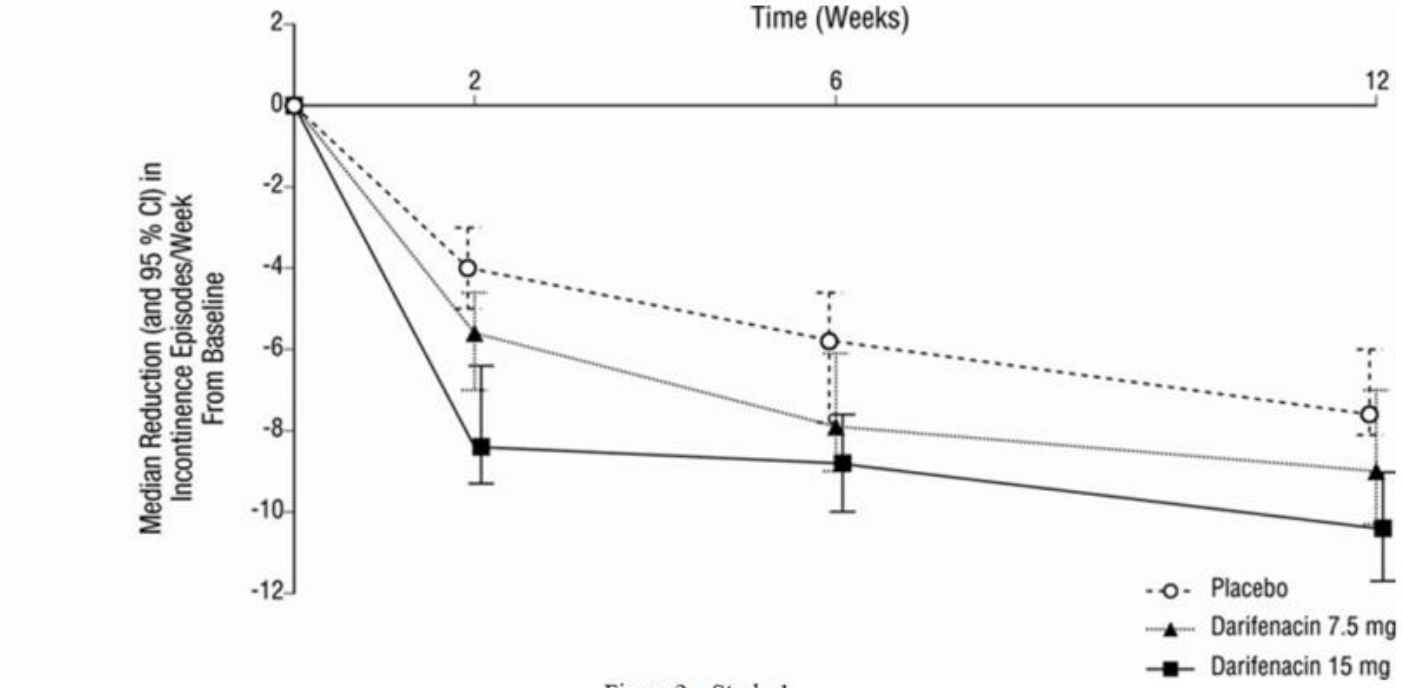


Figure 2a, Study 1

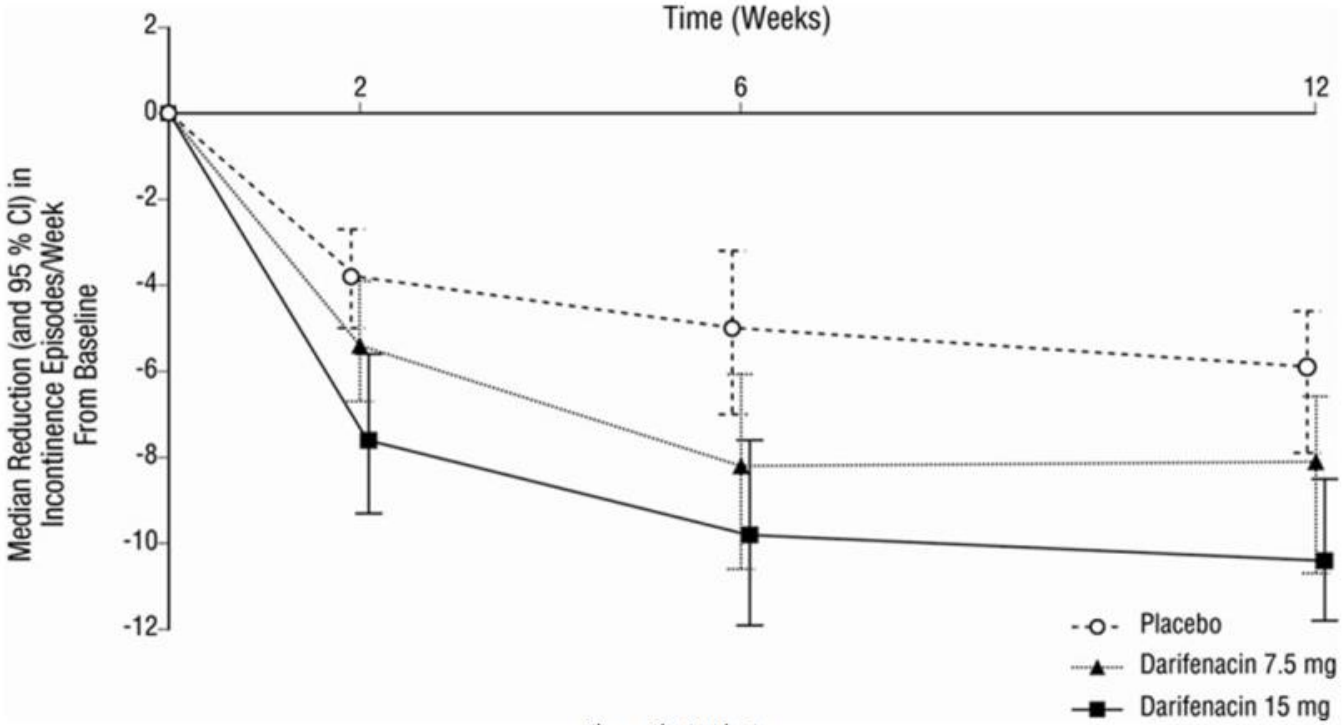


Figure 2b, Study 2

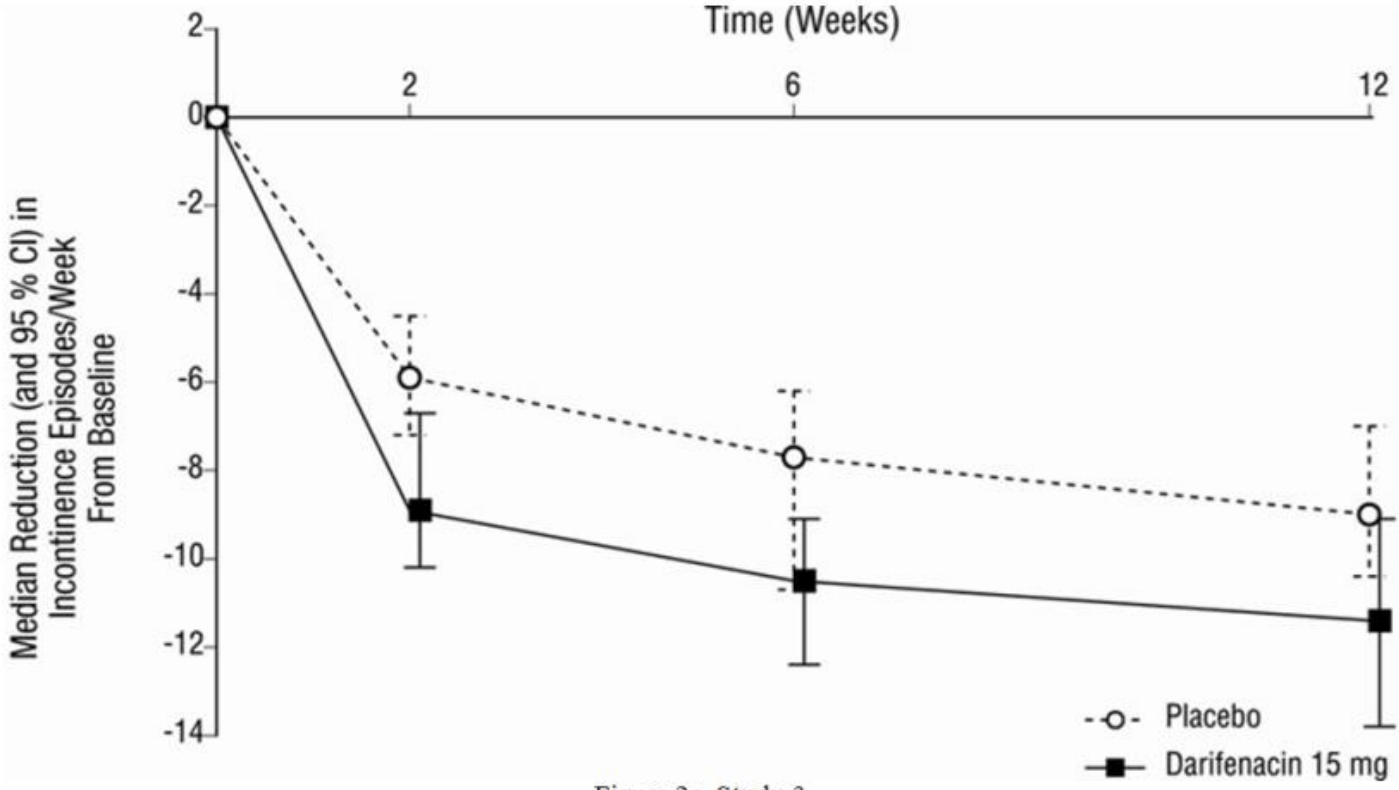


Figure 2c, Study 3

16 HOW SUPPLIED/STORAGE AND HANDLING

Enablex®, 7.5 mg are round, shallow, bi-convex, white-colored tablets, and are identified with “DF” on one side and “7.5” on the reverse.

Bottle of 30..... **NDC** 0430-0170-15

Bottle of 90..... **NDC** 0430-0170-23

Enablex®, 15 mg are round, shallow, bi-convex, light peach-colored tablets, and are identified with “DF” on one side and “15” on the reverse.

Bottle of 30..... **NDC** 0430-0171-15

Bottle of 90..... **NDC** 0430-0171-23

Storage

Store at 25° C (77° F); excursions permitted to 15 to 30° C (59 to 86° F) [see USP Controlled Room Temperature]. Protect from light.

Keep this and all drugs out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Patients should be informed that anticholinergic agents, such as Enablex, may produce clinically significant adverse effects related to anticholinergic pharmacological activity including constipation, urinary retention and blurred vision. Heat prostration (due to decreased sweating) can occur when anticholinergics such as Enablex are used in a hot environment. Because anticholinergics, such as Enablex, may produce dizziness or blurred vision, patients should be advised to exercise caution in decisions to engage in potentially dangerous activities until the drug’s effects have been determined. Patients should read the patient information leaflet before starting therapy with Enablex.

Patients should be informed that darifenacin may produce clinically significant angioedema that may result in airway obstruction. Patients should be advised to promptly discontinue darifenacin therapy and seek immediate medical attention if they experience edema of the tongue or laryngopharynx, or difficulty breathing.

Enablex extended-release tablets should be taken once daily with water. They may be taken with or without food, and should be swallowed whole and not chewed, divided or crushed.

FDA-Approved Patient Labeling

Enablex® (ĕn-ā-blĕx)
(darifenacin)
extended-release tablets

Read this Patient Information leaflet about Enablex® before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or your treatment.

What is Enablex?

Enablex is a prescription medicine for adults used to treat the following symptoms due to a condition called overactive bladder:

- Urge urinary incontinence: a strong need to urinate with leaking or wetting accidents
- Urgency: a strong need to urinate right away
- Frequency: urinating often

It is unknown if Enablex is safe and effective in children.

Who should not take Enablex?

Do not take Enablex if you:

- are not able to empty your bladder ("urinary retention")
- have delayed or slow emptying of your stomach ("gastric retention")
- have an eye problem called "uncontrolled narrow-angle glaucoma"

What should I tell my healthcare provider before starting Enablex?

Before starting Enablex, tell your doctor if you:

- have trouble emptying your bladder or if you have a weak urine stream
- have any stomach or intestinal problems, or problems with constipation
- have liver problems
- have any other medical conditions
- are pregnant or are planning to become pregnant. It is not known if Enablex can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Enablex passes into breast milk and if it can harm your baby. Talk to your doctor about the best way to feed your baby if you take Enablex.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Enablex and certain other medicines may affect each other, causing side effects.

Especially tell your healthcare provider if you take a:

- antifungal medicine ketoconazole (Nizoral®) or itraconazole (Sporanox®)
- antibiotic medicine clarithromycin (Biaxin®)
- anti-HIV medicine ritonavir (Norvir®) or nelfinavir (Viracept®)
- medicine to treat depression nefazadone (Serzone®)
- medicine to treat an abnormal heartbeat flecainide (Tambocor™)

- antipsychotic medicine thioridazine (Mellaril®)
- medicine to treat depression called a tricyclic antidepressant

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist each time you get a new medicine.

How should I take Enablex?

- Take Enablex exactly as prescribed. Your doctor will prescribe the dose that is right for you. Take Enablex 1 time daily with water.
- Enablex should be swallowed whole. Do not chew, cut or crush Enablex tablet.
- Enablex may be taken with or without food.
- If you take too much Enablex call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking Enablex?

Enablex can cause blurred vision or dizziness. Do not drive or operate heavy machinery until you know how Enablex affects you.

What are the possible side effects of Enablex?

Enablex may cause serious side effects including:

- Serious allergic reaction. Stop taking Enablex and get medical help right away if you have:
  - hives, skin rash or swelling
  - severe itching
  - swelling of your face, mouth or tongue
  - trouble breathing

The most common side effects with Enablex are:

- constipation
- dry mouth
- headache
- heartburn
- nausea
- urinary tract infection
- blurred vision
- heat exhaustion or heat-stroke. This can happen when Enablex is used in hot environments. Symptoms of heat exhaustion may include:
  - decreased sweating
  - dizziness
  - tiredness
  - nausea
  - increase body temperature

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Enablex. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store Enablex?

- Store Enablex at room temperature, between 59° F to 86° F (15° C to 30° C).
- Keep Enablex out of the light.

Keep Enablex and all medicines out of the reach of children.

General information about Enablex.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Enablex for a condition for which it was not prescribed. Do not give Enablex to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about Enablex. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Enablex that is written for health professionals.

What are the ingredients in Enablex?

Active ingredient: darifenacin

Inactive ingredients: dibasic calcium phosphate anhydrous, hypromellose, magnesium stearate, polyethylene glycol, talc, titanium dioxide.
The 15 mg tablet also contains ferric oxide red and ferric oxide yellow.

Distributed by:

Allergan USA, Inc.

Irvine, CA 92612

PRINCIPAL DISPLAY PANEL

NDC 0430-0170-15

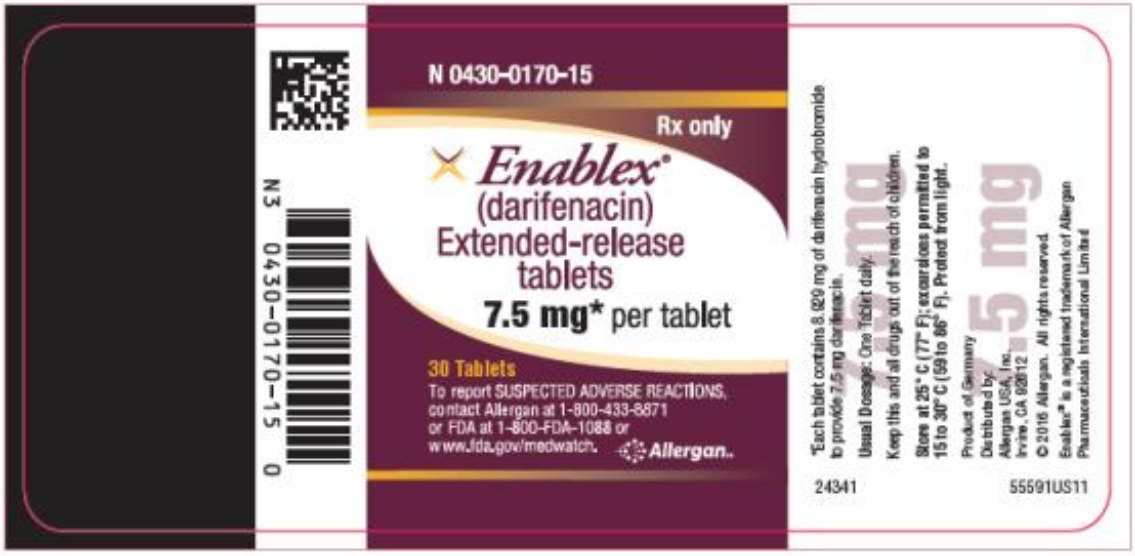
Rx only

Enablex® (darifenacin) Extended-release tablets

7.5 mg* per tablet

30 Tablets

To report SUSPECTED ADVERSE REACTIONS,
contact Allergan at 1-800-433-8871
or FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch.



PRINCIPAL DISPLAY PANEL

NDC 0430-0171-15

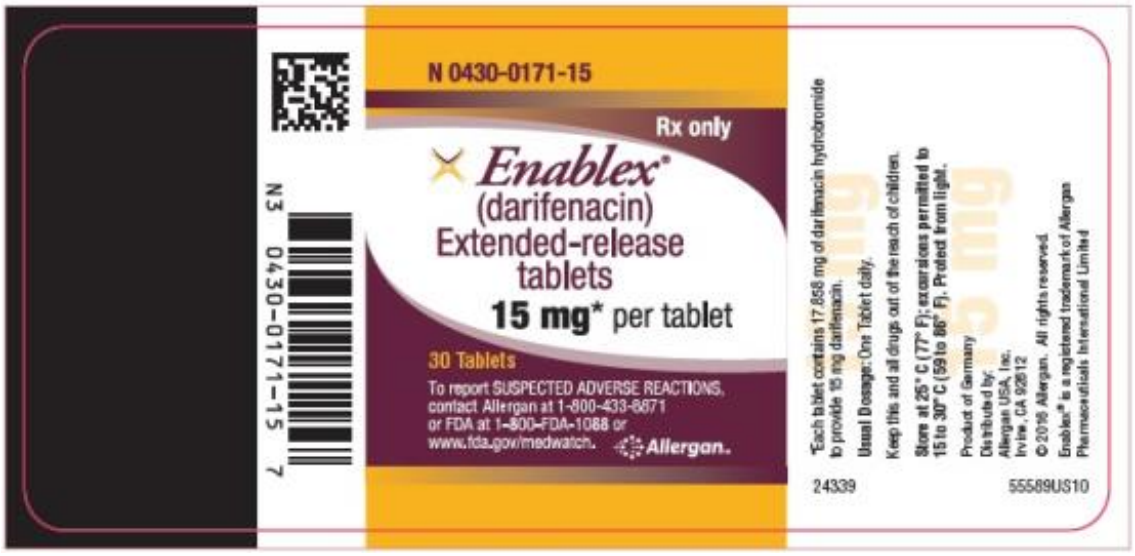
Rx only

Enablex® (darifenacin) Extended-release tablets

15 mg* per tablet

30 Tablets

To report SUSPECTED ADVERSE REACTIONS,
contact Allergan at 1-800-433-8871
or FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch.



PRINCIPAL DISPLAY PANEL

BULK

ENABLEX 7.5MG Ctd Tab US WE
Material: 0170X03
CiWOS Ident-Etikett
gem. Prozessauftrag

Master Label Standard

Version: 001

Materialbezeichnung / Material description:

ENABLEX 7.5MG Ctd Tab US WE

Material / Material:

0170X03

Etikett / Label:

CiWOS Ident-Etikett

Codierung Charge / Auftrags-Nr.
Coding Batch / PO-Number:

gem. Prozessauftrag

Etikett / Label:

Ausbeute-Etikett

Codierung Charge / Auftrags-Nr.
Coding Batch / PO-Number:

gem. Prozessauftrag

PRINCIPAL DISPLAY PANEL

BULK
ENABLEX 15MG Ctd Tab US WE
Material: 0170X02
CiWOS Ident-Etikett
gem. Prozessauftrag

Master Label Standard

Version: 001

Materialbezeichnung / Material description:

ENABLEX 15MG Ctd Tab US WE

Material / Material:

0171X02

Etikett / Label:

CiWOS Ident-Etikett

Codierung Charge / Auftrags-Nr.
Coding Batch / PO-Number:

gem. Prozessauftrag

Etikett / Label:

Ausbeute-Etikett

Codierung Charge / Auftrags-Nr.
Coding Batch / PO-Number:

gem. Prozessauftrag

ENABLEX

darifenacin tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0430-0170
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DARIFENACIN HYDROBROMIDE (UNII: CR02EYQ8GV) (DARIFENACIN - UNII:APG9819VLM)	DARIFENACIN	7.5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS DIBASIC CALCIUM PHOSPHATE (UNII: L11K75P92J)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 200 (UNII: R95B8J264J)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	DF;7;5
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0430-0170-96	1 in 1 CARTON	12/22/2004	05/31/2021
1		7 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:0430-0170-00	337500 in 1 DRUM; Type 0: Not a Combination Product	12/22/2004	05/31/2021
3	NDC:0430-0170-15	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/22/2004	05/31/2021
4	NDC:0430-0170-23	90 in 1 BOTTLE; Type 0: Not a Combination Product	12/22/2004	05/31/2021

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021513	12/22/2004	05/31/2021

ENABLEX

darifenacin tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0430-0171
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DARIFENACIN HYDROBROMIDE (UNII: CR02EYQ8GV) (DARIFENACIN - UNII:APG9819VLM)	DARIFENACIN	15 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS DIBASIC CALCIUM PHOSPHATE (UNII: L11K75P92J)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 200 (UNII: R95B8J264J)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	

Product Characteristics			
Color	ORANGE (light peach)	**Score**	no score
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	DF;15
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0430-0171-96	1 in 1 CARTON	12/22/2004	01/31/2021
1		7 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:0430-0171-00	337500 in 1 DRUM; Type 0: Not a Combination Product	12/22/2004	01/31/2021
3	NDC:0430-0171-15	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/22/2004	01/31/2021
4	NDC:0430-0171-23	90 in 1 BOTTLE; Type 0: Not a Combination Product	12/22/2004	01/31/2021

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021513	12/22/2004	05/31/2021

Labeler - Allergan, Inc. (144796497)